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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,112	08/23/2001	Stephen Donovan	D-2875DIV	1929

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,112	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE f this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25,36,37 and 67-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25,36,37 and 67-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 21-25, 36, 37 and 67-80 are pending.

Applicants' preliminary amendment filed on August 23, 2001 (Paper No. 2) has been entered. Claims 1-20, 26-35 and 38-60 have been cancelled, and new claims 67-80 have been added. Therefore, claims 21-25, 36, 37 and 67-80 are examined.

Claim Objections

2. Claim 76 is objected to because of the use of the term "producing a genetic construct having codes for botulinum toxin", use of "producing a genetic construct encoding a botulinum toxin" is suggested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 21-25, 36, 37, 67-77, 79 and 80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for obtaining an agent for alleviating pain, the method comprising producing a genetic construct having nucleic acids encoding a clostridial neurotoxin component, wherein H_C is removed or modified to reduce its ability to bind to receptors at the neuromuscular junction, and covalently attaching the clostridial neurotoxin component to a targeting moiety of substance P; or the method comprising producing a genetic construct having nucleic acids encoding a fusion protein of the described clostridial neurotoxin component and substance P; or a plasmid encoding a polypeptide from a clostridial

neurotoxin, comprising a nucleotide sequence encoding substance P and a translocation domain (H_N chain) of a clostridial neurotoxin, and a nucleotide sequence encoding the proteolytic domain (L chain) of a clostridial neurotoxin; or a method of making the polypeptide from a clostridial neurotoxin using the plasmid, does not reasonably provide enablement for a method for obtaining an agent for alleviating pain, the method comprising producing a genetic construct having nucleic acids encoding a clostridial neurotoxin or a modified clostridial neurotoxin component, and covalently attaching the modified component or the clostridial neurotoxin to a targeting moiety of a transmission compound or a substantially similar component; or the method comprising producing a genetic construct having nucleic acids encoding to a fusion protein of a modified clostridial neurotoxin component and a transmission compound; or a plasmid encoding a polypeptide from a clostridial neurotoxin, comprising a nucleotide sequence encoding a transmission compound and a translocation domain of a clostridial neurotoxin, and a nucleotide sequence encoding the proteolytic domain of a clostridial neurotoxin; and a method of making the polypeptide from a clostridial neurotoxin using the plasmid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 21-25, 36, 37, 67-77, 79 and 80 encompass a method for obtaining an agent for alleviating pain, the method comprising producing a genetic construct having nucleic acids encoding a clostridial neurotoxin or a modified clostridial neurotoxin component, and covalently attaching the clostridial neurotoxin or the modified component to a transmission compound or substance P (claims 21, 22, 67-77); or a method comprising producing a genetic construct having nucleic acids encoding a fusion protein of a modified clostridial neurotoxin component and a

transmission compound or substance P (claims 23-25, 79 and 80); or a plasmid encoding a polypeptide from a clostridial neurotoxin, comprising a nucleotide sequence encoding a transmission compound and a translocation domain of a clostridial neurotoxin, and a nucleotide sequence encoding the proteolytic domain of a clostridial neurotoxin (claim 36); and a method of making the polypeptide from a clostridial neurotoxin using the plasmid (claim 37). The specification, however, only discloses cursory conclusions (page 18) without data supporting the findings, which state that the agent for alleviating pain comprising a recombinant fusion protein of a clostridial neurotoxin or a clostridial neurotoxin component and a targeting moiety, or comprising a recombinant clostridial neurotoxin component chemically coupled to a targeting moiety. There are no indicia that the present application enables the full scope in view of the method of making the agent comprising a clostridial neurotoxin or a clostridial neurotoxin component and a targeting moiety as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the modified clostridial neurotoxin or fragments in the clostridial neurotoxin component, and a

transmission compound or a substantially similar component as the targeting moiety, which are not adequately described or demonstrated in the specification.

(2). The presence of working examples:

There is no working example indicating the claimed variants or methods in association with the claimed invention. Example 1 merely indicates the coupling of L chain from botulinum toxin B and H_N chain from botulinum toxin A to produce LH_N, and the agent comprising the clostridial neurotoxin fragments can be produced by recombinant technique.

(3). The state of the prior art and relative skill of those in the art:

The prior art (Johnson et al., U. S. Patent 5,955,368) teaches a system to express clostridial gene construction in a clostridial host, which includes a plasmid being transferred from *E. coli* into clostridium species, and a useful host strain permitting high levels of expression of clostridial genes using the clostridial promoter. However, the reference does not indicate the expression of a fusion protein of a clostridial neurotoxin component and a transmission compound, and the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the modified clostridial neurotoxin or fragments in the clostridial neurotoxin component, and the transmission compound as the targeting moiety to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a method for making an agent for alleviating pain, and the agent comprises a fusion protein of a clostridial neurotoxin or a clostridial neurotoxin component and a targeting moiety, or a clostridial neurotoxin component expressed

recombinantly and chemically coupled to a targeting moiety. The specification only indicates recombinant techniques are used to produce an agent comprising a specific targeting moiety such as substance P and a clostirdial neurotoxin component, wherein H_C is removed or modified to reduce its ability to bind to receptors at the neuromuscular junction, e.g., an agent of L-H_N and substance P (pages 23 and 30-31). However, the specification has not identified any other modified clostridial neurotoxins or fragments besides the modified H_C in the clostridial neurotoxin components, nor has demonstrated the making and use of the agent containing the modified clostridial neurotoxin or fragment and a transmission compound other than substance P. Moreover, the specification has not shown the making of an agent containing a clostridial neurotoxin having H_C chain and a transmission compound, and the use of this agent for treating pain. There are no working examples of these methods demonstrated in the specification. Furthermore, the specification does not provide teachings on the preparation and use of the agents containing various transmission compounds or their substantially similar components and various modified clostridial neurotoxins or fragments. Since the specification fails to provide sufficient guidance on the structural variation of modified clostridial components and transmission compounds, it is necessary to have additional guidance and to carry out further experimentation to assess the preparation and use of these agents.

(5). Predictability or unpredictability of the art:

The claims are directed to the preparation of agents containing various modified clostridial neurotoxins and various transmission compounds for alleviating pain, however, the specification has not identified these variants. Since the claims encompass many variants, the invention is highly unpredictable regarding the preparation and the effect of these agents.

(6). Nature of the Invention

The scope of the claims includes many structural variants in the agent for alleviating pain, but the specification does not identify these variations in the clostridial neurotoxin component and targeting moiety, nor demonstrates the use of the agent. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the guidance and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the preparation and the effects of the agents in alleviating pain.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 21-25, 36, 37 and 67-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-25, 36, 37 and 67-80 are indefinite because of the use of the term "a genetic construct having codes for a clostridial neurotoxin", "a modified clostridial neurotoxin and fragments thereof", "host organism" or "components substantially similar to the transmission compounds". The term "a genetic construct having codes for a clostridial neurotoxin", "a modified clostridial neurotoxin and fragments thereof", "host organism" or "components substantially similar to the transmission compounds" renders the claim indefinite, it is unclear what molecule the genetic construct has, use of the term "a genetic construct having nucleic

acids encoding a clostridial neurotoxin" is suggested. It is unclear from the claim how and where the clostridial neurotoxin is modified and what the fragments are as to "a modified clostridial neurotoxin and fragments thereof"; which host organism is intended, e.g., is it a host cell, or, a host organism which would include multicellular or unicellular eukryocytes and unicellular prokaryotes; how different the components are from the transmission compounds as to "substantially similar". Claim 21 is also indefinite because of the use the term "the clostridial neurotoxin component" in step (c) and "the clostridial neurotoxin" in step (d), it is not clear whether the clostridial neurotoxin component or the clostridial neurotoxin is expressed and covalently attached to a targeting moiety. Claims 22, 24, 25, 37, 68-75 and 80 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

5. Claims 36 and 37 are indefinite because of the use of the term "derived from" or "a therapeutic element having biological activity". The term "derived from" or "a therapeutic element having biological activity" renders the claim indefinite, it is unclear how different the polypeptide derived from clostridial neurotoxin is as compared to the parent clostridial neurotoxin, what the therapeutic element is, and what biological activity the therapeutic element has.

6. Claims 67-71, 79 and 80 are indefinite because of the use of the term "a clostridial component". The term "a clostridial component" renders the claim indefinite, it is unclear what the clostridial component is, e.g., is it L chain, H_N chain, or L-H_N. Claims 68-71 and 80 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Conclusion

7. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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October 30, 2002